To establish a *prima facie* case of obviousness, three basic criteria must be met. First there must by some suggestion or motivation, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, to modify the reference teachings. Second, there must be a reasonable expectation of success, and third, the prior art references must teach or suggest all the claim limitations. MPEP 2143. Applicants submit that the Examiner has not satisfied any of these criteria.

None of the references, alone or in combination, teach or suggest treatment of MM by administering an anti-alpha4 integrin antibody, such as an anti-VLA4 antibody, or an antigen binding fragment thereof. There is also no suggestion or motivation, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, to modify the teachings of Nakamura, Masellis-Smith and Lockhorst to arrive at the claimed methods. Nakamura *et al.* used anti-IL-6 receptor antibodies (not anti-VLA-4 antibodies) in a mouse model of MM. However, the anti-IL6 receptor antibodies were <u>ineffective</u> in the absence of a chemotherapeutic agent. See Nakamura at col. 20, lines 23-35; and col. 22, lines 13-20 and 49-53, and Table 2. Thus even if anti-VLA-4 antibodies inhibit IL-6 (which Examiner reads Lokhorst to suggest), one would not expect anti-VLA-4 antibodies alone to effectively treat MM.

Dr. Gregory Mundy, in a Declaration submitted September 11, 2006 (attached as Exhibit A), in related U.S. Application No. 10/086,217 (the '217 application), also explained that a practitioner of ordinary skill in the art would not, for numerous other reasons, have believed anti-alpha4 antibodies, such as anti-VLA-4 antibodies, to be interchangeable with agents that inhibit the IL-6 pathway. The '217 application is a continuation-in-part of the present application, and Dr. Mundy is an inventor on both the '217 and the present application. Dr. Mundy explained at paragraph 7 of the Declaration that an anti-IL-6 receptor antibody will disrupt a multitude of pathways, as this receptor interacts with at least two different classes of ligands, one class being the gp130 ligands and the other class being the gp80 ligands. Thus one would not expect that an anti-VLA-4 antibody, which disrupts very different interactions as described below, could substitute for an IL-6 receptor antibody. Dr. Mundy also explained at paragraph 4 of the Declaration that the prior art did not teach that anti-IL-6 antibodies could be

used to treat MM. For example, Bataille *et al.* ("Biological Effects of Anti-Interleukin-6 Murine Monoclonal Antibody in Advanced Multiple Myeloma" *Blood* 86:685-691, 1995; Ref. AQ in the IDS submitted March 27, 2006) taught that anti-IL-6 antibodies were not effective at treating MM. Bataille *et al.* reported that patients with advanced MM did not achieve remission or improved outcome following treatment with murine anti-IL-6 monoclonal antibodies. Dr. Mundy also explained at paragraph 5 of the Declaration that anti-VLA-4 antibodies are believed to work through mechanisms that are independent of IL-6. Anti-VLA-4 antibodies kill myeloma cells by blocking direct interactions between myeloma cells and normal host cells in the bone marrow. When the myeloma cells cannot attach to the normal host cells, the myeloma cells die. There may be a concomitant decrease in IL-6 levels following administration of anti-VLA-4 (as suggested by the *in vitro* findings of Lokhorst), but this would be a byproduct and not the direct cause of myeloma cell death, nor the reason why the myeloma cells die. Thus in light of the prior art, one of skill in the art would not conclude that an anti-VLA-4 antibody could substitute for an IL-6 antibody or an IL-6 receptor antibody, or any other antibody that disrupts the IL-6 pathway, for the treatment of MM.

In view of the teachings in the art as described above, one of ordinary skill would have no reasonable expectation of successfully treating MM with an anti-alpha4 integrin antibody or antigen binding fragment thereof.

Applicants contend that the Examiner has not established a *prima facie* case of obviousness and therefore respectfully request that the rejection of the claims under 37 C.F.R. § 103 be withdrawn.

Applicants further contend that the present claims are in condition for allowance, which action is requested.

Enclosed is a $450 check to cover the fee for a Petition for Two-Month Extension of Time. Please apply any other necessary charges, or any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 10274-034001.

Respectfully submitted,

Date: October 15, 2002

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